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Bariatric Surgery in Diabetes Mellitus type 2: predictors of remission, outcome and guidelines

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RESUMO

Introdução: Em 2015, cerca de 415 milhões de pessoas a nível mundial eram diabéticas. Destas, 90-95% eram tipo 2.

A diabetes Mellitus tipo 2 é um estado metabólico crónico caracterizado por redução da síntese de insulina por parte das células beta pancreáticas, aumento da resistência periférica à insulina e redução das incretinas intestinais, culminando no aumento da glicose sérica.

O tratamento da diabetes Mellitus tipo 2 pode englobar desde alterações no estilo de vida até cirurgia bariátrica. Esta última modalidade mostra evidências de ser a intervenção mais eficaz para o controlo da diabetes a curto/longo prazo.

Os objetivos desta revisão são caracterizar as principais alterações, quer a nível estrutural quer hormonal, inerentes à cirurgia bariátrica e capazes de induzir melhoria no controlo dos níveis séricos de glicose a curto/longo prazo, comparar os resultados da cirurgia bariátrica com o tratamento conservativo preconizado para a diabetes Mellitus tipo 2 e validar as *guidelines* estabelecidas para o tratamento cirúrgico da diabetes. Além disso, avaliar as variáveis que alteram o prognóstico da cirurgia bariátrica e a eficácia dos scores existentes.

Métodos: 74 artigos, desde janeiro de 2009 até janeiro de 2019, foram selecionados do PubMed e *guidelines* de diferentes organizações internacionais, tendo como base os critérios de inclusão/exclusão estabelecidos.

Resultados: O aumento das hormonas intestinais, como o peptídeo semelhante ao glucagon 1, a redução de grelina e o *bypass intestinal* parecem ser as alterações associadas à cirurgia bariátrica que mais influenciam o controlo da diabetes pós-cirurgia.

A cirurgia bariátrica, para doentes com IMC superior ou inferior a 35 kg/m^2, é superior as medidas conservativas na resolução/controlo da diabetes Mellitus tipo 2. Cirurgias com características malabsortivas são mais eficazes, mas apresentam mais complicações a curto e longo prazo quando comparadas com cirurgias do tipo restritivas.

Duração da diabetes e tratamento prévio com agentes hipoglicémicos são consistentemente referidos como fatores de remissão. O valor do peptídeo-C pré-cirurgia poderá condicionar o resultado da cirurgia bariátrica, mas mais estudos são necessários.

Conclusões: A cirurgia bariátrica é uma modalidade de tratamento da diabetes mellitus tipo 2 com provas dadas em relação à sua eficácia, quer em termos do controlo da diabetes como da redução do peso. O mecanismo associado à sua eficácia parece ser uma combinação de fatores.

Um score com aplicabilidade no contexto clínico e com fatores demonstrados como sendo modificadores de prognóstico da cirurgia bariátrica deverá ser criado, no sentido de auxiliar na escolha da opção terapêutica mais eficaz para cada doente.

ABSTRACT

Introduction: Diabetes Mellitus type 2 is a chronic metabolic condition characterized by peripheral insulin resistance and inadequate production by the pancreatic beta-cells, and reduction of incretin levels, culminating in a hyperglycemic state.

Treatment for diabetes Mellitus type 2 ranges from lifestyle interventions to bariatric surgery.

The aims of this review paper are to highlight the main hypothesis for DMT2 remission after bariatric surgery, the application of this type of surgery in DMT2 patients, regardless of BMI, and validate the current guidelines with study outcomes. Also, analyze the variables that alter surgery outcome on diabetes type 2 and the current remission scores.

Methods: A literature review with 74 articles selected from PubMed and guidelines from different diabetes associations, based on exclusion/inclusion criteria was carried out. The articles were selected from 2009 to 2019.

Results: The increase of gut hormones, decrease of ghrelin and intestinal bypass are the alterations created by some bariatric surgeries that most influence the glycemic control.

Bariatric surgery, either in patients with Body Mass Index≥ or <35kg/m^2, has proven to be more efficient than conservative measures in controlling diabetes Mellitus type 2. Surgeries with malabsorptive features are superior in achieving weight loss and DMT2 remission, but are associated with more post-surgery complications, compared to restrictive procedures.

Duration of diabetes and use of hypoglycemic agents pre-surgery, excepted for metformin, are variables consistently associated with DMT2 remission. The current scores include variables with questionable influence on surgery prognosis, reducing their ability to predict outcome.

Conclusion: Bariatric surgery appears to be an important element in the treatment of diabetes Mellitus type 2, showing better outcomes compared to conservative interventions, either on weight loss or glucose control. The main mechanism for diabetes remission after surgery seems to be a combination of factors.

Defining a score with clinical applicability and factors consistently associated with remission, would improve selection of treatment for each individual and, therefore, diabetes control.

Key words: Human; Bariatric surgery; diabetes Mellitus, Type 2; incretins; body mass index; blood glucose;

ABBREVIATIONS:

National Institute for Health Care excellent: NICE;

Diabetes Mellitus type 2: DMT2;

Diabetes Mellitus: DM;

Body mass index: BMI;

Weight loss: WL;

Roux-en-Y Gastric Bypass: RYGB;

Fasting Glucose: FG;

Glycated Hemoglobin: HbA1c;

Low-density Lipoprotein: LDL;

Triglycerides: TG;

Systolic Blood Pressure: SBP;

Sleeve gastrectomy: SG;

Great curvature plication: GCP;

Glucagon-like peptide-1: GLP-1;

Peptide YY: PYY;

Gastric inhibitory polypeptide: GIP;

Cholecystokinin: CCK;

Gastric bypass: GBy;

Total body fat: TBF;

laparoscopic adjustable gastric banding: LAGB;

Gastric banding: GB;

Biliopancreatic diversion: BPD;

Intensive Medical Therapy: IMT;

C- Reactive Protein: CRP;

high sensitivity C-reactive protein: hs C-RP;

Medical Treatment: MT;

Homeostatic Model Assessment for Insulin resistance: HOMA-IR;

Diabetes Surgery Summit: DSS;

American Society for metabolic and Bariatric surgery: ASMBS;

American Diabetes Association: ADA;

International Diabetes Federation: IDF;

Randomized control-trial: RCT;

High-density lipoprotein: HDL;

Impaired glucose tolerance: IGT;

Oral antidiabetic: ODA;

Laparoscopic Sleeve Gastrectomy: LSG;

Laparoscopic Sleeve Gastrectomy with Duodenal- Jejunal bypass: LSG-DJB;

Vertical Banded Gastroplasty: VBG;

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INTRODUCTION

According to the National Institute for Health Care Excellent, NICE, diabetes Mellitus type 2, DMT2, is a chronic metabolic state characterized by peripheral insulin resistance, inadequate pancreatic insulin production and reduction of incretin levels, culminating in a hyperglycemic environment[1-3,]. In table I are presented the diagnosis criteria for DMT2 established by the International Diabetes Federation, IDF.

In 2015, 415 million individuals were living with DM, a much higher number compared to 108 million in 1980[4]. Of these 90-95% had DMT2[4,5]. The number of people expected to have DM by 2030 is presumed to reach 438 million[6] and 592 million by 2035[7], making this disease the biggest healthcare threat of the century[6]. In 2015, 13.3% of Portuguese, between 20-79 years, were diabetic and this disease is believed to be responsible for 3-4% of deaths in Portugal every year, but the mortality rate associated to DM is showing tendency to decrease[8].

DMT2 can have a negative impact on multiple organs and systems[9]. Complications can be divided into microvascular, affecting mainly the retina (proliferative or non-proliferative retinopathy), the kidneys (diabetic nephropathy) and the nerves (central, autonomous, peripheral and sensorimotor), and macrovascular (ischemic heart, cerebrovascular and peripheral vascular disease)[9,10]. Interventions aiming glucose control help prevent and minimize organ-damage associated to diabetes Mellitus, DM[10].

It's believed that obesity increases the risk of DMT2 by 80-85%[1,11,12]. In Portugal, 55.4% of diabetics are obese[8]. Almost every morbidly obese adult, define as Body mass index (BMI) ≥40 Kg/m^2 [13], has some level of impaired glucose tolerance, IGT, and 36% of these will evolve to DMT2 in 10 years[14]. Obesity is known to create a chronic state of low-grade inflammation and that can be a possible mechanism behind insulin resistance in people with excess weight. Also, increase of fatty acids and supression of adiponectin ara associated with obesity[11,15].

The standard treatment for DMT2 starts with lifestyle interventions, mainly appropriate diet and exercise, and then, if this isn't effective, moves on to oral/injectable therapy. The first drug introduced is usually metformin, with addition of a second oral medication if target glycated hemoglobin, HbA1c, is not achieved with the first and so on[16].

Weight Loss, WL, is a crucial element in the management of DMT2[1]. Decrease, of at least 5% of the initial weight, can improve complications associated with DMT2[17]. Conservative measures, aiming to control DMT2 and weight, usually produce moderate WL, 5-10% of baseline body weight, don't stop pancreatic β-cell decline and, at short-term, the patients tend to regain the weight lost[2,3,11].

Bariatric surgery was first designed to help on WL, but the first reports suggesting improvement of obesity comorbidities were presented in the ‘70s[18]. Nowadays, the superiority of bariatric surgery compared to conservative measures to treat not just obesity, but also associated metabolic disorders, such as DMT2, is undisputable[4] and these results can last long periods of time[19]. Roux-en-Y gastric bypass, RYGB, for example, is capable of reducing BMI, HbA1c, fasting glucose, FG, insulin resistance, triglycerides, TG, low-density lipoprotein, LDL, and systolic blood pressure, SBP, without major complications in most of the patients [20,21].

In the past, WL was the main alteration associating DMT2 remission to bariatric surgery, but modification on glucose levels usually happens within days after surgery, before significant WL. Mechanisms weight-loss-independent, as gut hormones modification, intestinal bypass and decrease of pro-inflammatory state have been reported, and may probably explain the positive impact of some bariatric surgeries in the course of DMT2[3,22].

OBJETIVES

The objectives of this review paper are to highlight the main hypothesis for DMT2 remission after bariatric surgery, focusing primarily in the gut hormones modifications, the application of this type of surgery in DMT2 patients, regardless of BMI, and validate the current guidelines with study outcomes. Also, because nowadays the main criteria for bariatric surgery is BMI, confront the information of different studies and verify if BMI is a predictor of remission and analyze other possible variables.

METHODS

Search strategy

The research platforms used for this review were PubMed and the IDF, NICE, American Society for metabolic and Bariatric surgery, ASMBS, and American Diabetes Association, ADA websites. The search went from December 2018 and January 2019 and was based on the following key word combination: “bariatric surgery” and “gastrectomy”, “diabetes mellitus type 2”, “body mass index”, “treatment outcome”; “Bariatric surgery” and “gastrectomy”, “diabetes mellitus type 2”, “remission factors”; “Bariatric surgery” and “gastrectomy”, “diabetes mellitus type 2”, “ghrelin” OR “GLP-1”.

Inclusion Criterion

For this review, inclusion criteria were the following: review articles and meta-analysis, guidelines and case control studies written in English or Portuguese dated from 2009 to 2019. The articles selected focus on outcome of DMT2 after Bariatric surgery, independently of BMI, mechanisms associated with DMT2 and remission factors. Guidelines chosen were based on the relevance of each institution on DM field.

Exclusion Criteria

In this review, articles in languages other than English or Portuguese, were excluded. Also, articles focusing only on the following theme weren’t selected: outcome or mechanism of bariatric surgery on obesity or other comorbidities different to DMT2, treatment of DM type 1, studies with patients under 18 years-old and studies comparing, especially when the inclusion criteria was BMI>35, just different types of bariatric surgery, without including a comparative group with conservative intervention.

Article Selection

Out of the first selection, based on mesh words, selection of type of articles and established data range (from January 2009 to January 2019), 52 articles were selected. Based on abstract, main focus and inclusion/exclusion criteria define previously, 38 articles were included in this review. 7 articles/guidelines from different DMT2 associations and ADA website were added.

From the selected articles, by consulting each bibliographic references, where the data range was still taken into consideration, 29 were selected and the final number of articles for this review are 74. The schematic article selection is represented on Figure 1. In the articles focusing on outcome, the main variables analyzed (when available) were: WL, remission definition and rate (partial/total), HbA1c and/or FG (parameters of glycemic control), number of medication required/patient.

RESULTS

The effects of Bariatric surgery on gut Hormones

The first theories reporting the mechanisms behind DMT2 remission after bariatric surgery emphasized in the hypocaloric state inherent to food restriction, which would lead to WL[11,16,23,24]. The main theory, the starvation-followed-by-WL[24,25], is supported by the fact that all types of bariatric surgery are able to improve glucose metabolism within days, mainly by increase of hepatic insulin sensitivity, which is associated with reduce food intake. Peripheral insulin sensitivity also improves, but only after decrease of ≥15% of baseline body weight[11]. However, this theory lacks on explaining why DMT2 remission varies depending on the type of bariatric surgery, even though some produce similar WL[11,24].

In a prospective non-blinded study with 45 patients divided equally in 3 groups, they're submitted to either RYGB, sleeve gastrectomy, SG, or great Curve Plication, GCP. One month after each surgery, WL was similar between interventions, but glucose levels decrease was more accentuated after RYGB[26]. Fasting glucagon-like peptide-1, GLP-1, levels were similar between surgeries at baseline, 1 and 12 months of follow-up, but after food intake, GLP-1 rose more with RYGB during the 12-months follow-up. Fullness GLP-1 increased similarly in the surgeries with restrictive features. One month after each surgery, fasting peptide YY, PYY, and ghrelin levels were identical between the groups of participants, but were more elevated with RYGB at 12 months[26].

In a study with 52 patients, all female, 3 surgical groups were formed: Gastric Banding (16 patients), GB, biliopancreatic diversion, BPD, (16) and Gastric plication, GP, (20) the last one a procedure with malabsorptive and restrictive features. They're placed in each surgery group based on individual contraindications for the other procedures. Age and duration of DMT2 were equal between groups. The patients were evaluated in three moments during follow-up: 2 days, 1 and 6 months after surgery. Improvement of anthropometric parameters, fasting blood glucose, FBG, and DMT2 happened after all surgeries, but was more pronounce in the BPD group. FBG alteration was primarily seen in the first month after BPD. GIP levels decreased mainly in the first month after BPD, and were steady at 6 months, contrarily to the levels after GP, which increased, and GB, which produced no alteration on GIP levels. GLP-1 levels started to increase 2 days after BPD and kept rising during the first month, with stabilization at 6 months of follow-up, opposite to levels after GB, which started to increase only after 1 month, and GP, which decreased during this period[27].

A prospective trial compared the outcome of 60 patients, all divided equally in 3 groups of intervention, during two years: RYGB+Intensive medical treatment, IMT, SG+IMT or IMT. Baseline GLP-1 levels, pmol/L, 60 minutes after food stimulation, increased from 2.0 to 12.5 in the RYGB+IMT group, 2.4 to 7.3 in the SG+IMT and in the IMT patients no change was seen during follow-up. [2] GIP levels, pmol/L, also after food intake, reduced during follow-up in the RYGB+IMT group (30.7 to 13.5), and levels differed significantly from the other two groups [2]. Levels of high sensitivity C-reactive protein, hs C-RP, dropped similarly in the two surgical groups and no change was reported in the IMT patients[2]

In a 2-years follow-up study with BMI<35 kg/m^2 as inclusion criteria, complete remission rates were 50% with gastric bypass, GBy, and 5.5% with SG. This rates were achieved with similar WL, but more accentuated waist reduction in the GBy patients. Insulin secretion was normalized with both surgeries during the follow-up, but insulin resistance, calculated using the Homeostatic model assessment for insulin resistance, HOMA-IR (glucose x insulin/22.5), decreased more in the GBy group, even though both surgeries induced reduction[25]. In terms of gut hormones, both surgeries had the same effect in PYY and GLP-1 levels 30 and 60 minutes after food ingestion, but SG patients had a decrease on PYY at minute 90. Fasting GIP levels were similar between surgeries, but SG patients had a significant increase 30 and 60 minutes after food stimulation. Fasting acyl ghrelin, AG, increased more after GBy in a 2 years period and experienced bigger reductions 30 and 60 minutes post-prandial also with GBy[25].

In the Malin et al. study (characteristics of the study in table number II), fasting and after food stimulation GLP-1, GIP and acyl ghrelin, AG, levels were similar between patients in remission and no-remission at 12 months, but GLP-1 levels after meal stimulation at 24 months were significantly superior in the “no-remission” group compared to “remission” patients. Hs-CRP, decreased more in the remission group at 12 and 24 months and this decline was associated with decrease of FG and increase of glucose-dependent insulin release during-follow-up. Also, at 2 years, was linked to normal β-cell function. Adiponectin levels had bigger elevations in the “remission” group and, at 12 months, correlated with reduction in android body fat, decrease hepatic insulin resistance, improvement of glucose-stimulated insulin secretion, and β-cell normal function[28].

A clinical trial with 24 patients, all with BMI over 40 kg/m^2, involved two types of procedures: RYGB or RYGB plus gastric fundus removal, RYGB- GF. Baseline characteristics and hormone levels were all similar. The patients were evaluated at 3 points: 3, 6 and 12 months after each procedure. BMI levels decreased similarly in the two groups and glucose levels mainly in the RYGB- GF at 12 months follow-up. Fasting ghrelin levels decreased 3 months after surgery in the

RYGB group, but increase beyond baseline until the end of the follow-up, contrarily to RYGB-GF that showed decrease during the entire follow-up. Post-prandial ghrelin levels were partly suppressed in both surgical groups. Fasting GLP-1 levels didn't change at any point of the study in both groups, opposite to post-prandial levels, which increase in both groups, primarily in the RYGB- GF group. Fasting and post-prandial PYY levels increased with the two interventions, but mainly in the RYGB-FG group, and earlier, especially post-prandial levels[29].

Remission Predictors

37 patients were selected for a retrospective trial aiming to compare RYGB and SG. 40% in the RYGB and 27% in the SG group achieved DMT2 remission. 12 and 24 months after each intervention, two groups were formed: patients in "remission" and "no-remission". At baseline, "non-remission" patients were older, used more ODA pre-surgery, had bigger DMT2 duration, lower fasting C-Peptide, percentage of TBF and insulin sensitivity. Higher baseline adiponectin and less use of medication were correlated with normal glycemic status 12 and 24 months after each surgery. Increase of baseline adiponectin levels 12 months after surgeries was associated with decrease android body fat, diminished hepatic insulin resistance, higher β-cell function and glucose-dependent insulin secretion[28].

Panunzi et al. analyzed different interventions in 727 patients during a 2-years period and defined shorter duration of diabetes, younger age, no use of hypoglycemic medication and lower levels of FG as general predictors of DMT2 remission 2 years after bariatric surgery. Baseline characteristics associated with glycemia change were pre-treatment glycemia levels, HbA1c and HOMA-IR. For HbA1c variation during the follow-up the baseline factors were triglycerides, waist circumference and glycemia levels. BMI was not considered a factor for remission but, analyzing BMI by intervals, BMI>40 kg/m^2 had a risk of remission of 2.9 compared to BMI≤35 kg/m^2 and no different was seem between BMI≤35 kg/m^2 and BMI 35-40 kg/m^2. Predictors of remission changed depending on the type of surgery. In purely restrictive procedures, diabetes duration, FG levels and need for medical treatment were inversely correlated with remission. In procedures with malabsortive features FG was the only predictor[30].

A retrospective study composed by 254 severely obese patients (47.6±9.1 kg/m^2) after RYGB operation, had a follow-up period of 3 years minimum. During the study, 81.9% of patients achieved either partial (69.7%) or complete remission (12.2%), define by ADA[31] (table III). Age <45, DMT2 duration≤5 years and HbA1<7.0% pre-operative were all define as good remission factors for complete remission. Patients with DMT2 duration ≤5 years or 6-10 years and HbA1c<7% or <8.5-10% were more likely to achieve partial remission than patients with DMT2 duration>10 years and HbA1c>10%, respectively. 12% of patients that achieved either complete/partial remission, relapsed during the duration of follow-up, in average 3 years after remission. The use of any hypoglycemic medication, excepted for metformin, was associated with probability of relapse[32].

Ramos-Leví et al. developed a 5-years study focusing on relapse and glucose variability, GV, in patients in remission 18-24 months after Bariatric surgery. The authors chose 24 patients in remission, 12 submitted previously to RYGB and 12 to single anastomosis duodeno-ileal bypass with SG, SADI-S. At 5 years, all the patients of the SADI-S group and 6 patients of RYGB were in remission. GV at 18-24 months was demonstrated to be higher in the patients submitted to RYGB that were in remission compared to SADI-S patients. Mean glucose levels (remission: 88 mg/dL compared to no-remission: 95.33 mg/dL), amplitude of variation from mean blood glucose, maximum blood glucose levels registered and percentage of time spent with glucose level>140 mg/dl were parameters higher in patients that weren't in remission at 5 years follow-up compared to remission. GV was showed in this study to be a good method to evaluate long term remission[33].

In a retrospective study conducted in Korea by Kim et al. analyzed the impact of types of reconstructions and stomach size in 403 patients with gastric cancer submitted to gastrectomy during an average period of follow up of 33 months and BMI 24.7 ±3.0 kg/m^2. Three types of procedures were analyzed: subtotal gastrectomy followed by gastroduodenostomy, Billroth I, subtotal gastrectomy followed by gastrojejunostomy, Billroth II, and total gastrectomy followed esophagojejunostomy, RYGB. Comparing outcomes, the groups of total gastrectomy and duodenal bypass had better results compared to the opposites groups, subtotal gastrectomy and without duodenal bypass, respectively, and these variables were statistically significant associated to resolution of DMT2. Analyzing remission factors in each type of surgery, reduction of baseline BMI and follow-up duration were always associated with remission[34].

In a study aiming to determine predictors of remission and relapse at 5 years after RYGB, 175 patients were evaluated. Of those, 61% achieved either total or partial remission at 1 year, 54% were in remission 5 years after surgery, 25% at remission in the first year relapsed and 31% never achieved remission during the study. The study formed three groups: the one at 5-years remission, 5-R, the ones that relapsed at 5 years, 5-Relapse, and the group that never achieved remission, 5-RN. The 5-R, at baseline, had less duration of diabetes, fewer ODA, better glucose control and insulin use, were expect to be woman and with more weight, but less abdominal fat. Analyzing body composition, patients at 5-R lost more weight and abdominal fat at 6 and 12 months compared to the 5-NR group and the amount of weight lost was a factor statistically significant when comparing the 5-R and the 5-Relapse. Importantly, even though during the follow-up all groups experience weight regain, the 5-Relapse group experienced a bigger gain, including fat mass. Levels at 1 year follow-up of HbA1c and FG were associated with 5-NR and patients that had partial remission or no remission at 1 year were less likely to achieve remission at 5 years [35].

Outcome

In a study comparing lifestyle and surgical treatment (type of intervention and number of participants – table II) during a two years period, the remission rate was 63.7% in the surgical group and 15% in the medical group. At baseline, the lifestyle group had better anthropometric parameters (BMI, weight and waist circumference) and older mean participants than the surgical group. 2 years later, percentage of WL (-22.4±10.8 versus -2.5±6.5, %), reduction of waist circumference (-16.0±9.1 compared to -1.3±11.9, %) and HbA1c (table II) levels were all parameters statistically improved by surgery compared to lifestyle interventions.[30] In other randomized study comparing RYGB and intensive lifestyle intervention, 19 patients in each group were evaluated during a period of 3 years. Baseline characteristics were similar. In the year 1, 11 patients in the RYGB group and 3 of the ILI achieved glucose parameters goals, decreasing to 8 at year 3 with RYGB and 0 in the ILI. At the end of follow-up, 58% of RYGB patients achieved HbA1c<7%, contrasting with 11% in the ILI. [36] HbA1c decreased primarily in the first year of follow-up in the RYGB group, with stabilization of this parameter during the following 2 years. FPG, WL, BMI, TBF, waist circumference and quality of life were all parameters improved mainly in the RYGB group[36].

In the Kashyap et al. trial, 24 months after starting each intervention, all groups dropped their mean HbA1c, particularly in the RYGB+IMT group (table II). Relapse from 12 to 24 months of follow-up occurred in all groups, but the most pronounce was with SG+IMT (table IV). Mean FG, weight and total body fat, TBF, were all parameters improved primarily in the surgical groups. TBF increased during follow-up in the IMT group and abdominal fat decreased mainly with RYGB+IMT and this was statistically significant compared to the other two interventions. The mean baseline percentage of patients using insulin was 46.3% and at 24 months, almost all patients in the surgical groups dropped out insulin, contrarily to the IMT group, which increased the percentage of users for 59%[2].

In a 5-years study with 60 patients with BMI≥35 kg/m^2, 3 groups, divided in 1:1:1 and randomized, were formed and submitted to different therapies: RYGB, BPD or medical treatment, MT. At baseline, all parameters were equal, but 82% were women. 5 years after each intervention, 50% of the surgical group achieved partial remission, mostly patients in the BPD group, and none achieved total remission (table IV). In the MT group no patient achieved partial/total remission. Independently of remission status, 42% of RYGB and 68% of BPD patients reached HbA1c≤6.5% during the 5 years follow-up without medical treatment, compared to 27% in the MT that achieved this target HbA1c, but with hypoglycemic medication. FG levels decreased in all groups, but primarily and statistically significant in the BPD group, and the same happen with HbA1c, insulin resistance, calculated by HOMA-IR, WL and waist circumference. 47% of the surgical group at baseline needed insulin±other hypoglycemic medication, but at the end of the follow-up period no insulin was prescribed for these patients and 87% of the surgical group didn't required hypoglycemic medication during the course of the study. Contrariwise, in the MT group the use of oral antidiabetic, ODA, and insulin increased during the follow-up[37].

In a randomized control trial, RCT, with 61 participants, three interventions were evaluated: RYGB, laparoscopic adjustable GB, LAGB and intensive lifestyle intervention, ILI. At year 2 of follow-up, the three interventions stopped and all patients started low ILI. Total and partial remission at 3 years were only obtain in the surgical groups and mainly with RYGB patients (table IV). Analyzing the glycemic parameters, the RYGB group was the one that suffered bigger declines from baseline in HbA1c levels and FPG, -66 mg/dL ($p<0.05$ compared to the other two interventions), followed by LAGB (table II). The percentage of WL, waist circumference and TBF was statistically greater in the RYGB group versus the other two interventions. The use of antidiabetic medication declined in the surgical groups, with 72% and 45% of the RYGB and LAGB patients, respectively, not requiring any hypoglycemic agent after 3 years of intervention. All patients in the ILI group required hypoglycemic drugs during follow-up[38].

In a prospective non-randomized study comparing the effect of RYGB and 2 medical interventions (GLP-1 analog or SGLTA inhibitor), 90 patients with class I obesity, equally divided in 3 groups of intervention, were followed during 1 year. The patients were allocated in each intervention group based on their preference after learning about them. Baseline characteristics were similar between groups, excepted for mean BMI, which was superior in the RYGB patients. In all groups, the patients maintain the therapy they were on before starting this trial. Clinically important weight lost, define as WL superior to 5% from baseline during 6-12 months of intervention, was observed in all patients in the RYGB group, 56.7% of the GLP-1 analog intervention group and in no patients in the SGLTA inhibitor group. HbA1c end–point was achieved in all patients submitted to RYGB and, even though the other two groups had reduction of HbA1c, no patient in the medical groups reached the ideal HbA1c (table IV). The number of hypoglycemic medication/patient reduced with RYGB and GLP-1 analog, but no significant decrease was watched in the third group[39].

In a prospective RCT with initial 1808 participants, Cummings et al. choose 43 patients with BMI 30-45 kg/m^2 and mildly uncontrolled DMT2 to be randomized and treated with one of two treatment options: RYGB or ILI (table II), for 1 year. At baseline, all variables were similar, except duration of DMT2, which was statistically superior in the RYGB group. During the follow-up, 11 of the initial patients dropped from the study, leaving the RYGB group with 15 participants and 17 in the ILI. The authors documented statistically better results in the RYGB group on diabetes remission and HbA1c levels (table II and IV) and ability to maintain these levels during follow-up. At baseline, 60% of RYGB patients were insulin users compared to 47% of ILI patients. After 1 year, the percentage of ILI patients was kept equal, opposite to the percentage in the RYGB group, which dropped to 21%, and all patients in surgical group dropped at least ≥1 hypoglycemic medication (average ODA/person at 1 year: 0.5±0.2 versus 1.2±0.2 in the ILI). Insulin resistance, calculated using HOMA-IR, and anthropometric parameters declined in both group, but more with RYGB[40].

A RCT comparing bariatric surgery, RYGB or SG, to IMT was designed to have 3 phases of follow-up: at 1, 3 and 5 years after each intervention. 150 patients with BMI 27-43 kg/m^2 and badly controlled DMT2 (table II) were selected to initiate this study, but only 89% completed it. Baseline characteristics were similar between the three groups, except for the percentage of women, superior in the SG group. At 12 months, 12% of the medical group, 40% of the RYGB and 37% of the SG achieved the main end-point, HbA1c<6 %, with or without hypoglycemic agents. At 3 years, 5%, 38% and 24% achieved the end-point, respectively, and lastly, at 5 years, the percentages remain the same excepted in the RYGB group, which decrease to 29%. Remission rates during follow-up were superior in the surgical group and relapse at 3 years was superior in the medical group (table IV). FG and HbA1c (table II) decreased significantly in the surgical group compared to the IMT group, especially in the first three months, and the levels remain stable during the study. Anthropometric parameters improved in bigger extend in the surgical group during the study, especially with RYGB. The percentage of excess body weight decreased much more in the surgical group after 1 year of intervention, 88% in the RYGB and 81% in the SG, compared to the surgical group, 13%. Excess weight regain at 3 years, define as increase of >5% of baseline weight, happen only in IMT patients (7 out of 43). Three years after each intervention, 69% of the RYGB and 43% on the SG group didn't need any hypoglycemic agent and at 5 years 45% and 40%, correspondingly, were still without any medication. Percentage of insulin users decreased in all groups during the 5 years follow-up, but was only statistically significant in the surgical group. The number of ODA/patient in the IMT group increased during follow-up[41,42,43].

Guidelines

In 2007 the first Diabetes Surgery Summit, DSS-I, was held in Rome with the aim of reviewing all the clinical data available about application of bariatric surgery on DMT2 and expand the research and use of this treatment option. In 2015, in the second DSS, with the help of 48 members from different countries, organizations and medical fields, it's developed a global clinical algorithm, including medical and surgery treatment, for the management of DMT2[4,44] The algorithm designed is showed on table V in the complementary section. The experts also defined contraindications for the use of surgery on the treatment of DMT2: DM type 1, unless the procedure is indicated for other reason other than diabetes, current use of drugs or alcohol, diminished comprehension of risks/benefits/outcome, uncontrolled psychiatric disease and/or low adherence to nutritional supplementation and long-term follow-up necessary after surgery[4,44].

The latest guidelines by IDF[4], NICE[5], ADA[45], and ASMBS[46] follow the same principles defined in the DSS-II meeting. Bariatric surgery is recommended in patients with BMI≥35 kg/m^2 and DMT2 after ineffective conservative measures and can be also suggested in patients with BMI between 30-35 kg/m^2 with uncontrolled glucose levels after intensive conservative measures, including use of injectable hypoglycemic agents. With BMI≥40 kg/m^2, surgery should be suggest, regardless of glucose control[47]. Interestingly, all cut-offs must be down 2.5kg/m^2 when apply to Asian patients, because patients of this nationality are exposed to more DMT2 risk with lower BMI[2,48,49]. In this population, the cause of DMT2 seems to be beta-cell dysfunction with late and diminished insulin secretion[7].

DISCUSSION

Mechanism of Bariatric surgery on DMT2 remission

Currently, the main hypothesis explaining the effect of RYGB in DMT2 pathophysiology are: ghrelin, upper or lower intestinal hypothesis.

The principle of the first theory is that ghrelin release is altered after RYGB due to lack of food contact stimulation. Ghrelin, a prodiabetic and orexigenic hormone[24,26], is produced mainly in the gastric fundus by the A cells, but it can also be secreted in the duodenum[15]. This hormone increases food intake and adipogenesis and is probably responsible for inhibit insulin secretion[3,15]. The circulating levels vary with BMI and weight oscillations[11,14,24]. In obese patients, total ghrelin tends to be diminished[11,14]. In diet-induce WL the levels rises [14,24], but after bariatic surgery, mainly the ones where exclusion of gastric fundus is included, is expected a reduction of this hormone[24,26]. AG, on the contrary, is increased in obese patients, during periods of fasting and fullness. This hormone seems to have a more powerful role in the appetite regulation than total ghrelin, mainly because of its action on the hypothalamic food initiation center. In a trial with 60 patients, analyzing just the surgical groups included, AG (fasting and post-prandial) and total ghrelin increased primarily with RYGB and SG, respectively, but the patients submitted to RYGB had bigger DMT2 remission rates with weight loss similar to SG patients[15]. Few studies reported that ghrelin levels had a tendency to return to baseline values within months[11,14,15]. This alteration seems to work negatively for WL after RYGB[26].

Chronaiou et al. showed that, by removing the gastric fundus, ghrelin and other gut hormones (in this case, post-prandial GLP-1 and PYY levels) vary[29]. The alterations of gut hormones postoperative seen in this study and others demonstrate that ghrelin isn't the only alteration, caused by bariatric surgery, that positively impacts DMT2. Surgeries that involve intestinal bypass are consistently associated with better outcome, with or without stomach manipulation, so other pathways must also be modified. Therefore, ghrelin hypothesis doesn't explain entirely the mechanism behind bariatric surgery, even though decrease of ghrelin levels plays some part.

RYGB is known to be superior to SG in inducing DMT2 remission and the upper or the lower intestinal theories can be possible explanations[22]. The upper intestinal (or foregut) hypothesis states that, if the nutrient doesn't contact with the duodenum and jejunum, then it can improve diabetes status[11,22,24,50]. Two possible explanations for this are the existence of a portal vein sensor pathway and/or intestinal gluconeogenesis. Analyzing GB and RYGB, the differences in DMT2 remission between the two types of surgeries can be eliminated if denervation of portal vein is induced[11,26]. According to animal models, when bypassing the proximal intestine, intestinal gluconeogenesis is increased, causing rise on glucose concentration in the portal vein, which is not seen after GB, a procedure without intestinal bypass[11].

The creation of big intestinal bypasses, without manipulation of the stomach size[24,51]or with gastric pouches bigger than the ones created in the standard RYGB[26,37], resulted in improvement of glucose levels, superior to control groups. This leads to conclude that bypassing the intestinal plays an important role on the positive effect of bariatric surgery on DMT2, but other factors can be involved.

The lower theory, or hindgut, is based on the gut hormones alterations created with the intestinal bypass. By altering the intestinal architecture, it speeds up the delivery of nutrients and increases the release of gut hormones, for example GLP-1[22,50]. This hormone is an incretin released from the L cells in the ileum[3]. Incretins are promptly released during food intake and have a half-life of minutes[3]. They work by stimulating glucose-dependent insulin secretion and their effect is more visible after oral food intake than IV administration[3,11]. GIP is also an incretin, but in its case, released from duodenum. After surgery, the increase of gut hormones seems to happen before meaningful BMI fall[22] and days after surgery[27]. Comparing between restrictive and malabsortive surgeries, improvement of incretins after food stimulation tends to happen mainly and faster with surgeries with malabsortive features, which are also associated with better remission rates[3,15,26,27].Even though increase of post-prandial GLP-1 tends to be link to remission, in a 2 years study, GLP-1 levels increased mainly in "no-remission" patients. This was probably due to pancreatic β-cell resistance to GLP-1 action[28]. GIP levels decreased with surgeries associated with high remission rates, BPD[27] and RYGB[2], or increased primarily with SG, rather than RYGB[25]. This can be probably explained by the intestinal manipulation inherent to malabsortive surgeries, which can reduce the production of this hormone, or by the increase efficiency of GIP, which tends to be decreased with DMT2.

Despite the fact that SG is a restrictive procedure, is also associated with increase of incretins[3,25], which is counterintuitive when others restrictive surgeries are evaluated[11]. This effect seems to happen due to an acceleration of food transit[11,13,26], that causes exaggerated GLP-1 release[11] but the results are inconsisting[11]. Still, SG tends to be less effective than RYGB in inducing DMT2 remission[25]. In the Lee et al. study, excepted for PYY 90 minutes after food stimulation, both GBy and SG produced the same effect on incretin levels, but factors associated with worst outcomes, such as insulin resistance, levels of resistin and abdominal fat, were linked mainly to SG[25].

Other theories are emerging such as adiponectin rise, an anti-inflammatory hormone[24,28], modification of small intestine microbiota, increase of bile acid concentration and diminished pro-inflammatory state[2,15,16,24]. Changes on lifestyle, particularly, alterations on the type of food ingested, prioritizing healthier choices, have been reported after SG and RYGB. The reasons seem to be the increase of anorexigenic gut hormones, revulsion symptoms that can be triggered when ingesting certain types of foods and/or reduced stimulation of reward areas, normally activated with food intake[11].

Predictors of remission

It has been established three models to predict remission of DMT2 after metabolic surgery: DiaRem, ABCD and Individualized metabolic surgery, IMS score[48]. The first was presented by Still et al. based on a retrospective study with 690 patients, all submitted to RYGB, and followed during 5 years[52]. It scores from 0 to 22 and the probability of remission is presented in intervals[52]. ABCD score was first proposed by Lee et al. after identifying 4 variables as independent DMT2 remission factors in a study with 63 patients, submitted to either RYGB or Sleeve Billroth II GBy[53]. The IMS score was constructed based on a retrospective study with 659 obese patients undergoing either RYGB or SG and followed for minimum 5 years. Opposite to the other two scores, the aim of this score is to guide the physician choice between RYGB and SG, depending on severity of DMT2 and safety[54,55]. All scores and each variables are presented in table VI.

Analyzing the variables included in the three remission scores, IMS and ABCD scores have "duration of DMT2" in common. This is a probable remission factor based on the principle that, in the early stages of the disease, obesity-induced insulin resistance has caused reversible β-cell dysfunction, but most of the insulin secretion is still normal[9,45,56]. If surgery is performed in this moment, changes in the insulin sensitivity induce stabilization of β-cell function, without bigger changes on glucose levels[57]. The rate of T2DM remission with bariatric surgery is been proven to be inversely related to the years of diabetes progression[9,26,30,32,55,56,58]. Advance-DiaRem, a score system based on DiaRem with addition of two variables, "duration of diabetes" and "number of ODA", has showed to be more accurate than DiaRem in predicting which patient will enter remission 1 year after bariatric surgery[59].

Insulin use was considered a bad prognosis factor by various studies, either at short or long-term [9,26,33,60,50,61]. Parikh et al. observed that only 20% of insulin users entered remission during the first six months after bariatric surgery, compared to 80% of patients that didn't use insulin preoperative[62]. Use and number of antidiabetic agents (oral/injectable), excepted for metformin, are predictors of bad outcome[9,60,32,58,61]. This is probably true, because the increase need of hypoglycemic agents represents a decrease of β-cell reservoir[32].

Anthropometric parameters weren't consistently associated to bariatric surgery outcome. Higher BMI at baseline was considered a predictor of good outcome in some studies[30,36,48,60,58] and others didn't acknowledge it[56,40]. In the Yan et al. study, 30 patients had BMI<24, meaning that this study can have different conclusions when compared to patients with BMI>35[58]. In a 3 years study, 40% of the participants had BMI 30-35 kg/m^2 and 60% BMI>35 kg/m^2 and the authors showed that, independently of the obesity class, the patients had the same results[38]. Weight variation, in some studies, wasn't associated with remission [37,42,56,63,40,50] or relapse[37,43]. On the contrary, WL after surgery was define as predictor of 1-year and long term remission in other studies[33,42,55]. Even though many studies acknowledged reduction of abdominal perimeter as a factor with bigger impact on remission, compared to the other anthropometric parameters, only one study proved the association of decrease abdominal fat and glucose control[2]. Upper body fat, emphasizing in the visceral fat, apparentely plays a big role on DMT2 evalution[11,15]. Visceral fat is known to be metabolically more active than subcutaneous fat, producing adipose-specific cytokines and pro-inflammatory cytokines[1].

High preoperative HbA1c levels was define as predictor of bad outcome[9,32,50,60] and is included in the IMS and ABDC score. Good baseline glycemic control, define by diminished levels of FG, HbA1c or no use of insulin pre-surgery, was acknowledged as predictor of good outcome[48,42] and the SOS study highlighted baseline glucose concentration, presence/absence of IG and HOMA-IR as factors linked to remission[56]. A rapid decrease of HbA1c after surgery was also define as predictor of remission at 1 year[61].

Baseline C-Peptide is only present at ABCD score as a variable associated with remission. Cheng et al. acknowledged fasting C-Peptide levels as the most important predictor of remission, because it reflects the reservoir of insulin in DMT2 patients[48,58]. Therefore, low levels are linked to worse control of glycemic status post-operative[48,53]. A meta-analysis conducted by Yan et al. affirmed the same, but had a small selection of articles and the percentage of insulin users and years of follow-up were very wide between studies, which could alter its conclusions[64]. In a study with inclusion criteria "BMI 30-35 kg/m^2", higher stimulated C-Peptide was defined as a remission factor at 24 months after surgery[7]. C-Peptide wasn't measure in many studies, so its validation as a remission factor was limited.

Patients with older age have less probability of entering remission[9,60], contrarily to the younger individuals[32,42,48,61]. Though, some studies didn't recognize "age" as a prognosis factor[37,40,65]. Gender was also not a variable consistent, with studies acknowledging male sex as a good remission factor[9], one study female sex, but only during the first year of follow-up[60] and other didn't even recognize gender as a remission factor at any point of follow-up[40].

Others likely to be remission factors not contemplated in any of the three scores, as for TG[37], type of surgery[51] or variation of GLP-1[26] require more studies, because, depending on the characteristics available/analyze in each study, the variables associated with outcome change and some variables aren't recognize, because they're not analyzed.

Reviewing the efficacy of score systems, ABCD was considered superior to DiaRem and IMS scores in comparing study[48,20]. One problem with the DiaRem score is it applicability, because the participants of the original trial had mean BMI of 48 kg/m^2 and were submitted only to GBy procedures. Not inclusion of duration of diabetes in the score also reduces its accuracy, based on the improvement of results with Advance-DiaRem. The IMS score lacks on exploring other type pf surgeries and the original conclusions could be altered if the number of participants submitted to the two types of surgeries analyzed was equal (in the original study, 78% in the RYGB group and 22% in the SG). The ABCD Score, even though it's aknowledged as the score with better efficiency, only includes results after gastric bypass surggeries and, compared to the other two scores, had a very small population size (63 patients) and lower follow-up period (3 years). Inclusion of BMI and not hypoglycemic agents (injectable/oral) can question its efficacy, based on the results presented in various studies.

Outcome

Bariatric surgery can be divided into three types of procedures: restrictive, malabsorptive and a combination of the two. In surgeries with restrictive features, the stomach size is reduced, without any alteration to the intestinal architecture[4]. Three examples of restrictive procedures are GCP, LAGB and SG[3]. In LAGB, a small adjustable bandage is placed around the proximal portion of the stomach in order to produce a reduction of its size, leaving approximately 30 mL volume in total[11]. During the SG procedure a gastric sleeve tube is formed by resecting from beyond the gastric incisura until the angle of His, reducing the volume of the stomach by 75-80% [3,4,22,26].

Malabsorptive procedures aim is to cause alterations on the absorption of nutrients by creating an intestinal bypass[4]. BPD, an example of these procedure, is based on the creation of a horizontal gastrectomy and anastomosis between the remain stomach and the distal part of the small intestine, excluding the duodenum, jejunum and part of the ileum[23].

RYGB is a mix procedure, combining restrictive features and malabsorptive. [3,22,26]. This surgery is based on the creation of a small gastric pouch, approximately of 30 mL volume, anastomosed to the jejunum, creating a bypass pathway. [3,22,11]

When comparing the outcome of the different types of bariatric surgery, is useful to separate the restrictive from the malabsortive surgeries. In one hand, the first ones are less capable of achieving long-term glucose control and improvement of metabolic comorbidities, but show less short and long terms complications, when related to malabsortive techniques[4,14,63,66].

In a meta-analysis comparing RYGB to conservative treatment during 12-60 months, bariatric surgery proved to be more effective in inducing DMT2 remission and changes on anthropometric parameters than to conservative treatment in obese patients at short and mild-term follow-up. [16] In the studies analyzed in this review with inclusion criteria BMI≥35 kg/m^2, complete DMT2 remission rates with bariatric surgery vary from 5-100% and with conservative measures from 0-14.4%. The range of remission rates was very wide because the studies had different follow-up time, number and selection of participants, baseline characteristics randomization, type of surgeries and conservative interventions and complete remission definition (tables 4 and 5). Bariatric surgery outperformed conservative measures in many parameters analyzed: anthropometric features, such as abdominal fat, TBF and BMI, HbA1c and FG [2,36-39]. The number of patients using insulin/hypoglycemic agents decreased also in almost every surgical groups, [16,37-39] with either stabilization or increase[2,37,39] in the respective comparative medical group. One important aspect is the probably of relapse, which happened in a few surgical groups[2,9,37,38,42,43]. In a 3 years study after RYGB 60% of patients achieved partial remission at 1 year, but this percentage reduced to 45% in year 2 and 40% in year 3[38]. Even though some patients tend to relapse after surgery, an aspect that a few studies have highlighted is that these patients maintain improvement on glucose levels at short/long term, when compared to baseline, but not sufficient to meet the remission criteria established[9,37,57]. In the SOS bariatric surgery was proven to be superior to conservative treatment in preventing the development of DMT2 in patients with moderate obesity and IGT or normal glucose levels pre-surgery[56]. This shows that, beyond inducing remission, bariatric surgery improves glycemic status in almost every patient, which by itself helps to prevent complications associated to DM[67]. So, probably, instead of focusing in remission rates, the success of bariatric surgery should be based on the grade of glucose decrease.

A relevant criterion for selection of diabetes treatment is the ability to reduce the incidence and severity of complications. In a study comparing RYGB to medical treatment, the risk of developing organ-damage associated with DM was inferior with RYGB, mainly microvascular complications. The incidence of total macrovascular complications was inferior in the RYGB group, though incidence of cerebrovascular and peripheral diseases was superior in this group[9]. In the same study, comparing patients that entered DMT2 remission and no-remission, the “remission” patients had an incidence of microvascular and macrovascular inferior to the “no-remission” group by 57% and 24%, respectively[9]. In other study, microvascular complications developed mainly in the medical group compared to BPD/RYGB during a 5 years follow-up[37] (table VII). Even though the number of new complications after Bariatric surgery tends to decrease, already established diabetic retinopathy doesn't seems to reduce or aggravate[43,67,68].

Metabolic control[38,39], improvement of lipid profile[16,37] and reduction of cardiovascular risk [37] all seem to improve more after bariatric surgery than conservative measures. Metabolic control (table VIII) was achieved by 13%, 68% and 100% of the patients in the MT, RYGB and BPD group, respectively, at 5 years in Mingrone et al study.[37] In a RCT with 43 patients, the surgical group also had better control over metabolic factors, including decrease of SBP and HbA1c and tendency to increase HDL levels [36,40]. The 10-year risk of fatal/nonfatal coronary heart disease, using United Kingdom Prospective Diabetes Study risk equation, showed big reductions after bariatric surgery compared to conservative measures[17,36,69]. Lipid profile doesn't change uniformly, with studies reporting improvement only on HDL[2], others on HDL and TG [36,43] and LDL, total cholesterol [16].

According to IDF, AMBS and ADA guidelines, patients obese class I can be candidates for bariatric surgery, but only after failure of conservative measures[4,45,46]. Remission rate after surgery in these patients' floats between 0-88% depending on DMT2 remission definition, population characteristics, follow-up time, BMI interval established and type of interventions[7,25,57,62,63,70,71]. Meta-analysis conducted in this topic show similar remission rates[72,65]. Other parameters were also improved after surgeries such as FG, HbA1c, need for hypoglycemic agents and HOMA-IR[62, 65,71]. Two studies disagree with this conclusion[57,70]. One study comparing open duodenal-jejunal exclusion surgery to ILI acknowledged only that surgery was superior to medical treatment on inducing HbA1c decrease. On the other parameters analyzed, optimization of ILI was able to achieve the same results surgery[70]. This study had as inclusion criteria baseline C-Peptide >1 ng/mL[70]. Other study, now comparing GB and metformin, had the same results and specific inclusion criteria: patients should have either impaired glucose tolerance or DMT2 diagnose <1 year[57]. These studies had small follow-up time (24 weeks [70]and 2 years [57], small populations (24 and 88) and the type of surgeries studied are not the most used, so, even though apparently patients with modest DMT2 don't benefit from bariatric surgery, more studies must be performed in order to have conclusions to apply on general population. Analyzing groups of patients with BMI above or inferior to cut-offs established by IDF, submitted to the same type of bariatric surgery, improvement of glucose levels is seen in both groups and equal rates of complications, though remission rates and weight loss tend to be superior when BMI>35/30 kg/m^2 [49,73]. This concludes that surgery's a valid and safe option compared to conservative measures for patients with BMI under 35 and DMT2. More research in this population must be done, because there is a lack of studies about this subject and, those that exist, have small populations and short follow-up time.

Anastomotic leakage and need for reconstruction, stenosis, gastroesophageal reflux disease, GERD, (if pre-surgery GERD exists, GB can deteriorate the condition), hernias, hemorrhages, ulcers, need for cholecystectomy, for example, are complications that health professionals should be alert postoperative[16,23,65,72-74]. Other complications are decrease of lean mass, especially reported after RYGB, with decreases that can go up to 10% from baseline, [36,38,40] and decrease of bone mass[23,38]. In surgeries with malabsortive features, micronutrients deficiency such as vitamins, calcium, iron and folate are frequently and, even though protocols exist to prevent this kind of deficits, they are still important problems after surgery (table VII). The dumping syndrome, characterized by nauseas, vomiting or hypoglycemic symptoms, is associated with accelerated gastric emptying or quick exposure of nutrients to the small intestine that occurs mainly after RYGB (can occur in up to 40% depending on the series), but also with restrictive procedures[74]. Quality of life parameters, such as general health, physical function, emotional well-being and energy, improved mainly from baseline with bariatric surgery[42,71].

Mortality rates of bariatric surgery are very low nowadays, ranging from 0-0.5%[21,45,72], similar to a cholecystectomy or hysteroscopy[4], due to introduction of laparoscopy and more experienced surgeons[21,45]. Major complications, such as cardiopulmonary events or thromboembolic disease, are reported in a frequency of 2-6%, but this events are known to be the cause of 70% of the deaths after surgery[21,45,50].

KEY LEARNING POINTS

Gut hormones after bariatric surgery

- Weight loss and food restriction aren't the only factors linking bariatric surgery to DMT2 remission[11,24].
- Mechanisms weight loss-independent, such as decrease of total/acyl ghrelin[24,26], increase of incretins [3,15,26,27], intestinal bypass[11,22,24,50] and rise of adiponectin[24,28], are all variables altered after bariatric surgery and possibly related with T2DM remission.

Guidelines

- Patients with BMI≥40 kg/m^2 should be offer bariatric surgery, regardless of glycemic control or number of hypoglycemic agents[45].
- Bariatric surgery can be recommended in patients with BMI 35-39.9 when conservative measures fails and can be suggested if good glucose control is achieved.
- In individuals with BMI between 30-35 kg/m^2 surgery can be suggested when optimize conservative measures are not effective on glucose control.
- All cut-offs must be down 2.5kg/m^2 if apply to Asian patients, because patients of this nationality are exposed to more DMT2 risk with lower BMI [48].

Outcome

- Bariatric surgery outperforms conservative measures on improvement of anthropometric parameters (weight loss, reduction of waist circumference and body fat) [2,37-39] and glucose control (HbA1c, FG, insulin resistance, reduction of hypoglycemic agents)[16,37-39].
- Bariatric surgery is associated with better metabolic control[38,39], lipid profile[16,37], reduction of cardiovascular risk[37] and prevention of organ-damage[9,37].
- Micronutrient deficiencies, anastomic leakage and need for reconstruction, stenosis, gastroesophageal reflux disease and dumping syndrome are probable complications after bariatric surgery[16,23,65,72,74].
- Mortality rate associated with surgery is very low, 0-0.5%, due to introduction of laparoscopic and train surgeons [19,72].

Predictors of remission

- Duration of T2DM[9,56], use of hypoglycemic agents pre-surgery and, possibly C-Peptide levels, are variables associated with surgery outcome.

- BMI or weight loss are not consistently linked to surgery outcome, so the actual use of BMI as criteria for inclusion/exclusion of patients for bariatric surgery is not appropriate [30,48,60,58].
- The IMS, ABCD and DiaRem scores fail in including variables inconsistently associated with surgery outcome[48,20].

CONCLUSION

This review acknowledges the use of bariatric surgery as a treatment option for obese patients and diabetics type 2, with the aim of better control or resolution of DM.

Bariatric surgery outperformed conservative measures in many points associated with improvement of weight and its comorbidities. DMT2 patients and obese class I apparently have benefits in doing bariatric surgery opposite to lifestyle interventions, but the current studies in this field have small populations and follow-up periods. So, for now, the decision to include these patients for surgery treatment must be individualize, balancing the pros and cons.

The existing theories that explore the main mechanism associating improvement of glucose control and bariatric surgery show some evidence, but doesn't seem to be just one pathway, but a combination of factors. Understanding the mechanisms involved is a positive step towards new lines of DMT2 treatment.

Duration of DMT2 and use of hypoglycemic agents pre-surgery were factors associated with outcome in many studies, opposite to BMI, with inconsistent results. In the future, creation of an algorithm with variables proven to influence surgery prognosis would be a relevant tool for medical teams in approaching DMT2 treatment.

COMPLEMENTARY SECTION

Table I- Criteria for DM diagnosis according to International Diabetes Federation

Criteria for DM diagnosis based on International Diabetes Federation
Fasting Plasma glucose (FPG) ≥126 mg/dL (≥7.0 mmol/L)
Oral glucose tolerance test (OGTT) at 2 hours ≥200 mg/dL (11.1 mmol/L)
Random plasma glucose in symptomatic patient ≥200 mg/dL (11.1 mmol/L)
HbA1c≥6.5% (48 mmol/mol)

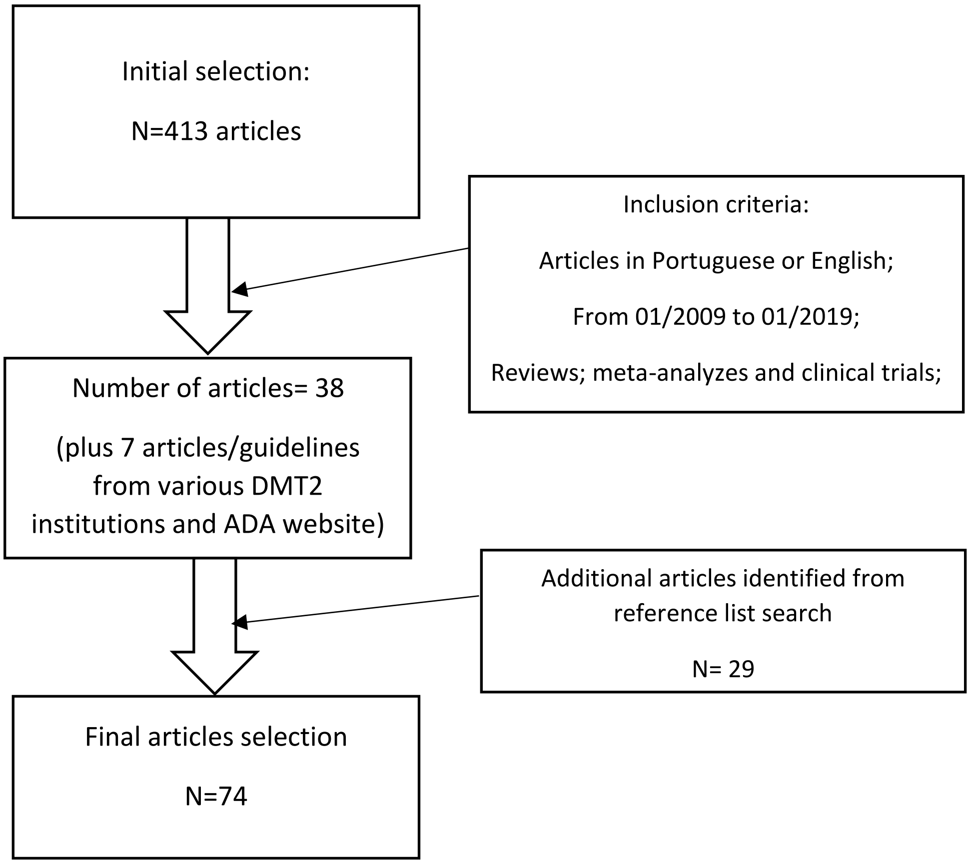

Figure 1- Articles selection methodology

Table II - Articles and correspondingly follow-up, number of participants, type of interventions and changes of baseline characteristics (HbA1c and BMI)

Reference	N	Type of interventions	Follow-up time (years: y; months: m)	Mean Io BMI (kg/m^2)	Mean Final BMI (kg/m^2)	Mean Io HbA1c, %; FG (mg/dl)	Mean Final HbA1c, %; FG (mg/dl)
Panunzi et al.[30]	727	Surgical Group: RYGB, 77, BPD, 20, GB,91, and VBG, 227 (415 in total) Medical treatment group: diet and exercise (312 patient)	2y	Surgical group: 42.0±5.0 Medical group: 40.1±4.9	Surgical group: 32.4±5.0 Medical group: 39.0±4.9	Surgical group: 8.3±1.5 Medical group: 8.0±1.4	Surgical group: 5.8±1.0 Medical group: 7.2±1.0
Xiang et al.[57]	88	Surgical Group: GB Medical Group: metformin Randomized 1:1	2y	Surgical group: 35.7±2.9 Medical group: 35±29	Surgical group: 35.7±2.9 Medical group: 34.8±2.8	mmol/mol Surgical group: 41.2±4.6 Medical group: 40.1±4.5	Surgical group: 41.5±4.5 Medical group: 40.8±4.6
Kashyap et al.[2]	60	Surgical Group: RYGB or SG Medical Group: Intensive Medical Treatment Randomized 1:1:1	2y	Surgical group: RYGB: 36.1±2.6 SG: 36.4± 3.2 Medical group: 35.8±3.0	Surgical group: RYGB: 27.4±2.9 SG: 28.2±2.9 Medical group: 35.6±3.1	Surgical group: RYGB: 9.8±1.35 SG: 9.7± 1.95 Medical group: 9.5±1.73	Surgical group: RYGB: 6.7±1.23 SG: 7.1±0.84 Medical group: 8.4±3.3
Parikh et al.[62]	57	Surgical group: RYGB, SG and GB: 29 patients; ILI (diet, exercise and ODA): 28 patients	6m	Surgical group: 32.8 ILI: 32.4 (mean)	Surgical group: 25.9 ILI: 31.4 (mean)	Surgical group: 7.4 ILI:7.7 (mean)	Surgical group: 6.2 ILI:7.8 (mean)

Schauer et al.[42]	150	Surgical group: RYGB or SG ILI Randomized 1:1:1	3y	Surgical group: RYGB: 37.0±3.3 SG: 36.2±3.9 Medical group: 36.8±3.0	(not reported) % of WL: Surgical group: RYGB: -24.5±9.1 SG: -21.1±8.9 Medical group: -4.2±8.3	Surgical group: RYGB: 9.3±1.4 SG:9.5±1.7 Medical group: 9.0±1.4	Surgical group RYGB: 7.3±1.5 SG: 7.4±1.6 Medical group: 8.5±2.2
Cummings et al.[40]	43	Surgical group: RYGB ILI: ≥ 45 minutes of aerobic exercises 5 days/week, diet focused on glucose levels improvement and optimized medical therapy	1y	Surgical group: 38.3 ILI group: 37.1 Mean Weight (kg) Surgical group: 108.8 ILI group: 112.8	BMI not reported Mean Weight (kg) Surgical group: 80.7 ILI group: 105.6	Surgical group: 7.7±1.0 ILI group: 7.3±0.9	Surgical group: 6.4±1.6 ILI group: 6.9±1.3
Carlsson et al.[56]	3456	Surgical group: 1685 participants total 311 GB; 207 GBy; 1140 VBG; Medical group: 1771 participants	15y	Surgical group: 42.4±4.5 Medical group: 40.2±4.7		HbA1c levels not reported Blood glucose (mg/dL) Surgical group: 80.3 ±10.8 Medical group: 79.0± 11.0	

Mingrone et al.[37]	60	Surgical group: RYGB or BPD Medical treatment Randomized in 1:1:1	5y	Surgical group: BPD: 44.7 RYGB:44.0 Medical group: 45.4	Surgical group: BPD: 30.3 RYGB:31.3 Medical group:42.1	Surgical group: BPD: 8.9 RYGB: 8.7 Medical group: 8.5	Surgical group: BPD: 6.4 RYGB: 6.7 Medical group: 6.9
Courcoulas et al.[38]	61	Surgical group: RYGB: 21 patients LAGB: 20 patients ILI: 20 patients	3y	Surgical group: RYGB: 35.67 LAGB: 35.58 ILI: 35.75	Surgical group: RYGB: 26.97 LAGB: 30.39 ILI: 34.0	Surgical group: RYGB:8.5 6 LAGB:7.8 7 ILI: 7.03	Surgical group: RYGB:7.1 4 LAGB:7.0 7 ILI: 7.24
Bhandari et al.[39]	90	RYGB: 30 patients Medical group: GLP-1 analog: 30 patients SGLT2 inhibitor: 30 patients	12m	RYGB: 34.1±0.65 Medical group: GLP-1 analog: 32.65±1.1 SGLT2 inhibitor: 31.4±0.75	RYGB: 27.4±1.3 Medical group: GLP-1 analog: 30.88±1.1 SGLT2 inhibitor: 31.3±0.7	RYGB: 8.1±0.53 Medical group: GLP-1 analog: 7.6±0.5 SGLT2 inhibitor: 7.8±0.63	RYGB: 5.7±0.6 Medical group: GLP-1 analog: 7.2±0.3 SGLT2 inhibitor: 7.8±0
Simonson et al.[36]	38	RYGB: 19 patients ILI, including hypoglycemic agents: 19 patients	3y	RYGB: 36.0 ILI: 36.5 (mean)	RYGB: 27.3 ILI: 34.7 (mean)	RYGB:8.2 4 ILI: 8.78 (mean)	RYGB:6.4 5 ILI: 8.39 (mean)

Table IIII- Criteria for partial, complete and long-term remission established by ADA

	Definition according to ADA Consensus[31]
Partial Remission	HbA1<6.5%, FG 100-125 mg/dL for at least one year without hyoglycemic medication
Complete Remission	HbA1c<5.6% and FG<100 mg/dL for at least one year without hyoglycemic medication
Long-term remission	Complete remission for at least 5 years

Table IV- Remission definition, rate of remission and relapse according to articles included in this review

References	Definition of DMT2 remission	% of patients in remission	Relapse
Panunzi et al.[30]	FG<5,6 mmol/L without ODA or insulin	(at 2 years) Surgical group: 63.7% Medical group: 14.4%	Not documented
Kashyap et al.[2]	End-point: HbA1c≤6.0%	Surgical groups: RYGB: 33.3%; SG: 11% Medical Treatment: 6%	15% from year 1 to year 2 in the SG group
Cummings et al.[40]	HbA1c<6% with no antidiabetic mediation at least for a year	Surgical group: 60% ILI group: 5.9%	Not documented
Schauer et al.[41-43]	HbA1c<6.5% without hypoglycemic treatment	Surgical group (3,5 years): RYGB: 46%; 31% SG: 22%; 23.4% Medical group (3,5 years): 0%; 0%	Relapse at 3 years (HbA1c<6% at year 1 but not at 3 years): Surgical group: RYGB: 24% SG: 50% Medical group: 80%.
Mingrone et al.[37]	Complete remission: FPG≤5.6 mmol/L plus HbA1≤6.5% without medication for 1 year; -Partial remission: FPG 5.6-6.9 mmol/L plus HbA1≤6.5% without medication for 1 year	1. Complete remission: Surgical group: BPD: 0% RYGB: 0% Medical group: 0% 2. Partial remission: Surgical group: BPD: 63% RYGB: 37% Medical group: 0%	Relapse: hyperglycemia at 5 years after achieving partial remission at 2 years: Surgical group: BPD: 37% RYGB: 53% Medical group: 0%
Courcoulas et al.[38]	Complete remission: HbA1c<5.7% plus FPG≤100 mg/dL and no medication ≥1 year; Partial remission: HbA1c<6.5% plus FPG≤125 mg/dL and no medication ≥1 year	1.Complete remission: RYGB: 15% LAGB: 5% ILI: 0% 2. Partial remission: RYGB: 25% LAGB: 24% ILI: 0%	Relapse: 20% in the RYGB group from year 1 to 3
Bhandari et al.[39]	Remission: HbA1c<6.5%	RYGB: 100%; Medical group: GLP-1 analog: 0%; SGLT-2 inhibitor: 0%;	Not documented

Madsen et al.[9]	Complete remission: HbA1c<6.0% with only metformin as hypoglycemic agent or HbA1c<6.5% without any medication	RYGB: At 5 years: ≥70%;	Relapse: HbA1c>6.5% or a prescription for a hypoglycemic agent after initial discontinuation between year 1 and year 5; 27% from the RYGB
Simonson et al.[36]	Remission: HbA1c<6.5% and FPF<126 mg/dL	RYGB: 42.1% (without hypoglycemic medication: 36.8%) ILI: 0%	Relapse (from year 1 to 3): 16% (3/19) in the ILI and 21% in the RYGB (4/19);

Table V- Algorithm for Bariatric surgery in patients with DMT2 according to DSS-II

Patients with DMT2	
Obese BMI≥30 kg/m^2 (or ≥27.5 if Asian Patient)	Non obese BMI<30 kg/m^2 (or <27.5 if Asian Patient) • Non-surgical treatment
<u>Obese class I</u> BMI 30-34.9 kg/m^2 (or 27.5-32.4 if Asian Patient) • *First Line*: Optimal lifestyle and medical interventions (including injectable hypoglycemic agents and insulin) • *Second line if optimal glucose control is not achieved with conservative measures:* suggest bariatric surgery	
<u>Obese class II</u> BMI 35-39.9 kg/m^2 (or 32.5-37.4 if Asian patient) • *First Line*: Optimal lifestyle and medical interventions • *Second line if optimal glucose control is not achieved with conservative measures:* recommend bariatric surgery • *Alternative if optimal glucose control is achieved with conservative measures:* Suggest bariatric surgery	
<u>Obese class III</u> BMI≥40 kg/m^2 (or 37.5 if Asian Patient) • Recommend bariatric surgery	

Table VI- Remission scores (IMS, ABCD and DiaRem score)

	Score		
	IMS Score[55]	*ABCD Score*[53]	*DiaRem Score* [52]
Variables	Duration of DMT2	Duration of DMT2	Baseline HbA1c
	Number of hypoglycemic agents pre-surgery	C-Peptide Levels at baseline	Type of hypoglycemic medication
	Glycemic control, define as HbA1c<7%	Age	Age
	Insulin Use	BMI at baseline	Insulin Use
Score and Probability of Remission, (%)	Mild DMT2: ≤25	10-9	0-2: 88-99%
		8-7	3-7: 64-88%
	Moderate DMT2: 26-95	6-5	3-7: 64-88%
		4-3	8-12: 23-49%
	Severe DMT2 >95	2-0	13-17: 11-33%
			18-22: 2-16%

Table VII- Article, corresponding follow-up period, type of interventions and complications associated with each intervention

Characteristics of study / Reference	Follow-up (years ,y; months, m)	Medical Treatment ± Lifestyle Interventions [number of patients]	Bariatric surgery (the type of surgeries included in the study) [number of patients]
Mingrone et al.[37]	5y	Major complication: [1] fatal acute myocardial infarction; Diabetes complications: Development of [1] retinopathy; [1] nephropathy; [2] neuropathy Minor complications: Persistent diarrhea associated with the use of metformin; --- No metabolic complication associated	(RYGB and BPD) No major complication Early complications: [1] incisional hernia requiring surgery with BPD; [1] intestinal obstruction with RYGB; Diabetes complications: Development of [1] nephropathy after RYGB; Minor complications: [2] hypoglycemia events with RYGB; --- Metabolic complications: BPD [5] Iron deficiency anemia; [3] Hypoalbuminemia; [3] Osteopenia; [2] Renal calculus; RYGB [3] Iron deficiency anemia; [1] osteopenia; [1] renal calculus.
Yan et al.[16]		Major complications: [1] fatal acute myocardial infarction; Metabolic complications: reported 62.63% patients; [39] hypoglycemic events; [7] renal calculus; [6] anemia; More episodes of depression compared to the surgical group;	(RYGB) Major complication: [1] jejunojejunosyomy leakage, that led to anoxic brain injury, lower extremity amputation and long-term disability; Minor and metabolic complications: reported in 80.4% patients [11] anemia; [35] hypoglycemic events; [4] intestinal obstructions; [8) anastomotic ulcer;
Casajoana et al.[26]	12m	---	Major complications: (RYGB) [1] hemoperitoneum; [2] gastrojejunal and ileoileal anastomotic hemorrhages;

			(GCP) [1] hemoperitoneum; Early complications: (SG and RYGB) [2] intra-abdominal collection; (SG) [1] wound infection; (GCP) [2] vomiting and [1] gastroesophageal reflux.
Xiang et al.[57]	2y	(metformin) Minor gastrointestinal symptoms.	(GB) Major complications: [2] band slippage with the implication of removal; [1] cholecystectomy due to acalculous cholecystitis.
Cummings et al.[18]	1y	(Intensive lifestyle intervention) No major complications [64] minor complications: [39] hypoglycemic events; [4] severe hypoglycemic events; [7] musculoskeletal complaints.	(RYGB) No major complications; [31] minor complications: [16] hypoglycemic events; [0] severe hypoglycemic events; [2] musculoskeletal complains.
Geloneze et al.[70]	24 weeks	ILI No major complications; Minor complications: Hypoglycemic episodes in 83% patients.	(ODJS) No major complications; Minor complications: [2] wound infections; [10] Persisting nauseas during the first 2-4 weeks; [3] Hypoglycemic events; [6] Vomits.
Carlsson et al.[56]	15y	———	(GB; GBy; VBG) Major complications: [3] deaths within 90-days post-operative; [16] thromboembolism; [79] pulmonary complications; Minor complications: [53] vomits; [35] wound infections; [18] hemorrhages; [23] anastomotic leakages, peritonitis or abscess.
Schauer et al.[43]	5y	(intensive lifestyle and medical intervention) Major complications: [1] fatal myocardial infarction; Minor complications: [1] GI ulcer; [3] Episodes of	(SG and RYGB) Complications in the SG group: [1] Stroke; [1] GI ulcer; [13] Gastroesophageal reflux disease; [4] Episodes of

		dehydration; [9] Gastroesophageal reflux disease; [7] Anemia; [39] Hypoglycemic events; [6] Renal calculus; [6] Nephropathy; [4] Neuropathy; [11]Depression.	dehydration; [1] Dumpling syndrome; [2] Retinopathy; [9] Nephropathy; [5] Renal calculus; [2] Foot ulcer; [5] Neuropathy; [24] Anemia; [40] Hypoglycemic events; [12] Depression; [3] Wound infection; Complications in the RYGB group: [4] GI ulcer; [5] Gastroesophageal reflux disease; [2] Intra-abdominal bleeding; [7] Episodes of dehydration; [4] Dumpling syndrome; [1] Retinopathy; [11] Nephropathy; [6] Renal calculus; [2] Foot ulcer; [1] Neuropathy; [14] Anemia; [32] Hypoglycemic events; [2] Severe hypoglycemic event; [1] Ketoacidosis.

Table VIII- Metabolic control criteria by IDF

Metabolic Control by IDF (presence of ≥2 criteria)
Reduction of hypoglycemic medication ±
Reduction of baseline HbA1c ≥20% ±
Systolic Blood Pressure (SBP)<135 mmHg ±
Diastolic Blood Pressure (DBP)<85 mmHg ±
LDL<2.3 mmol/L

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